Remarks

Please reconsider this application in view of the requested amendment to the claims, the enclosed Terminal Disclaimer and the following remarks.

This application includes 59 claims (1-29, 31-37 and 39-61). Claim 1 is herein amended to add a recitation that it uses a method selected from mathematical decomposition, time-series analysis, mathematical modeling, computer modeling, signal processing, statistical analysis, and methods of artificial intelligence, and a combination of mathematical decomposition with methods of artificial intelligence. Claim 3, which depends from claim 1, is amended to delete the recitation of the methods that have been inserted in the parent claim. Claim 20 is amended in a manner similar to the amendment of claim 1. Small editorial amendments have been made to claims 21, 23, 24, 25, 34 and 59 to correct redundant recitations and provide proper antecedents to the claims. Claim 30 is withdrawn without prejudice.

The Official Action rejects all the claims in this application under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 of U.S. Patent 6,925,324, claims 1-29 of U.S. Patent 6,389,308 and claims 1-48 of copending application 11/642,268. A Terminal Disclaimer is enclosed herewith to overcome that rejection.

Paragraph 5 of the Official Action rejects Applicant's claims 7, 9, 10, 11, 20, 22, 23, 24, 32, 34, 36, 37, 38, 39-48, 50-52, 57, 58, 60 and 61 under 35 U.S.C. 102(b) as being anticipated by Selker et al. (5,724,963.

Selker et al. 5,724,983 discloses a system for continuous monitoring a cardiac patient 18 using an electrocardiograph 10, a waveform analyzer 12, a predictive instrument 14 and a control module 16. The waveform analyzer is programmed to analyze ECG waveforms and recognize the presence of certain characteristics that are particularly indicative of the cardiac condition of the patient. The predictive instrument 14 uses the output of the waveform analyzer 12 in conjunction with other clinical information about the patient and computes a probability that the patient has a life-threatening cardiac condition. The patent notes that the electrocardiograph and the waveform analyzer are commercially available as a single unit. The waveform analyzer is not time sensitive, meaning that it is a static statistical

analysis. The system can also include a detector 58 that receives the computed probabilities from the predictive instrument and looks for significant changes in the computed probability. However, only a few, simple types of changes, such as changes in the amplitude or rate of change, can be detected by comparing the data with simple thresholds. Please note that Applicant co-authored an article in 1994 entitled Building and Application of Expert Systems For Differential Diagnostics of Cardiovascular Diseases, which discloses a statistical diagnostic system similar to the disclosure in Selker et al. 5,724,983 (see the Invention Disclosure Statement by Applicant in this application).

The Official Action states that the "function of the waveform analyzer is considered to be analogous to the low level resolution analysis performed by applicant's invention. The result of the waveform analysis is then output to the prediction instrument that uses a higher level of analysis, such as statistical analysis, to predict the medical condition of the patient."

Applicant respectfully submits that while the waveform analyzer and the predictive instrument in the reference might be considered as low level and higher level analysis, there are several important differences between Applicant's invention and the Selker et al. disclosure. These differences include:

(1) The higher resolution analysis with Applicant's invention does not attempt to predict the probability of a patient having a particular cardiac condition. Instead, Applicant's higher resolution identifies subtle serial changes and the abnormal or unstable primary elements using analysis of the time series (i.e. serial measurements) of primary elements. The Selker et. al predictive instrument does not analyze the time series of primary elements. Thus, the Selker et al. predictive instrument might be considered to provide a higher level analysis as compared to the waveform analyzer, but it is not a higher level resolution to detect small serial changes in the primary elements.

(2) Selker et al. teaches snapshot measurements of primary elements at each point in time with an immediate inclusion of such snapshot measurements into a predictive instrument, which calculates a probability of a disease (i.e. cardiac condition) using a **standard, linear regression**. Note that in Selker's et al. Figure 2, which shows variables (i.e. clinical or ECG indicators) and their respective coefficients used for linear regression, only a single coefficient is used for each variable. The time series or serial changes in these variables are neither detected nor analyzed. By contrast, in Applicant's invention, **serial**

changes in the primary elements are represented by a plurality of coefficients. The mathematical tools used by the Applicant to obtain a plurality of coefficients representing serial changes in the primary elements (i.e. an orthogonal decomposition, pattern recognition, and time-series analysis) are quite different from the standard linear regression taught by Selker et al.

(3) Applicant's higher level resolution analysis is not limited to a single snapshot measurement or to comparison of the current snapshot with a previous one taught by Selker et al. In the Applicant's disclosure and claims, the higher resolution analysis might include >2 (and even >100) **serial measurements. Analysis of such complex, multi-point time series** is qualitatively different from the standard statistical analysis described by Selker et al. Applicant's time series analysis must include multiple coefficients (instead of a single coefficient for each variable as taught by Selker et al.) obtained using special mathematical tools described in the Applicant's application. These mathematical tools and their application are not trivial, and different applications and modifications of these tools have been a subject of several publications by the Applicant in high-profile scientific Journals, including Circulation and Circulation Research, which only accept highly novel studies.

(4) The analysis by Selker et al. can only detect the types of changes that are selected a-priori by a human developer of this algorithm. Selker et al. teach in column 10, lines 1-17 as follows:

> "Standard, well known regression techniques may be employed to identify the most appropriate set of explanatory variables, namely, the x.sub.i 's, and to determine the values of the coefficients of these variables. For a description of such techniques and examples of commercially available computer programs that implement them, see N. C. Cary in SUGI Supplement Library User's Guide, SAS Institute, p. 181-202, 1983, and L. Engelman, "PLR Stepwise Logistic Regression," BMDP Statistical Software, Chap. 14.5, pp. 330-334, BMDP publishers, Westwood, Calif. Of course, the precise set of explanatory variables that are identified and the predictive ability of the resulting logistic equation generally depends upon the quality of the underlying data that is used to develop the model. Such factors as the size and completeness of the database are often of significant importance. The selection of the relevant variables and the computation of the appropriate coefficients are well within the skill of an ordinary person skilled in the art."

In contrast to Selker et al, Applicant's high-level resolution analysis is not limited to a-priori predetermined types of changes. Applicant uses mathematical tools which automatically determine any types of changes that

occur in the time series of primary elements and thus identify subtle or unusual changes of any type as well as unstable time series of primary elements, which are impossible to analyze by Selker's et al. method.

(5) The Selker et al. method only determines some a-priori selected types of changes, whereas Applicant's method can characterize the structure of serial changes completely (Mathematical completeness means that no changes will be missed and all significant changes will be detected). This quality stems from the theoretical properties and the non-trivial way of applying the mathematical tools for serial analysis discovered by Applicant. The validity of these tools and their superior performance in detecting subtle serial changes, which would be missed by other standard statistical techniques (including those used by Selker et al.) has been proven by the Applicant in a number of publications in high-ranking scientific Journals listed below.

Applicant's Publications:

Shusterman V, Goldberg A, London B. Upsurge in T-wave alternans and nonalternating repolarization instability precedes spontaneous initiation of ventricular tachyarrhythmias in humans. Circulation 2006;113(25):2880-7.

Shusterman V, Goldberg A, Schindler DM, Fleischmann KE, Lux RL, Drew BJ. Dynamic tracking of ischemia in the surface electrocardiogram. J Electrocardiol. 2007

Lampert RJ, Soufer R, McPherson CA, Batsford WP, Tirado S, Earley C, Goldberg A, Shusterman V. Implantable cardioverter-defibrillator shocks increase T-wave alternans. Journal of Cardiovascular Electrophysiology, 2007;18:512-517.

Shusterman V, Aysin B, Anderson KP, Beigel A. Multidimensional rhythm disturbances as a precursor of sustained ventricular tachyarrhythmias. Circulation Research, 2001;88:705-712.

Shusterman V, Usiene I, Harrigal C, Lee JS, Kubota T, Feldman AM, London B. Strain-specific patterns of cardiac rhythm, autonomic nervous system activity, and susceptibility to heart failure in mice. American Journal of Physiology – Heart and Circulatory Physiology 2002; 282: H2076-H2083.

Shusterman V, Jannetta PJ, Aysin B, Beigel A, Glukhovskoy M, Usiene I. Direct mechanical stimulation of brainstem modulates cardiac rhythm and repolarization in humans. J of Electrocardiology 2002; 35: 247-256.

Shusterman V, Aysin B, Ermentrout GB, London B, Schwartzman D. Detecting instabilities of cardiac rhythm. J of Electrocardiology 2003; 36: 219-226.

Shusterman V, Goldberg A. Tracking repolarization dynamics in real-life data. J of Electrocardiology 2004:37:180-186.

Examples Demonstrating the Differences Between Applicant's Method and That of Selker et al.

Following are two examples that illustrate the difference between the Applicant's method from that of Selker et al. The first example (Figure 1) shows time series of consecutive amplitudes of the ST-segment in the electrocardiogram (ECG) obtained from a patient who presented to the Emergency Department with chest pain. The amplitude of the ST-segment is the primary diagnostic indicator used for monitoring the presence of cardiac ischemia, a potentially life-threatening abnormality. The figure shows that the time series has a complex structure due to the presence of artifacts and multiple uncontrolled factors (including changes in body position, respiration, movements, etc.). Thus, a simple threshold-based ischemia detector described by Selker et al. would not produce reliable results in most cases of continuous monitoring. In other words, the methods of Selker et al. would only work in an ideal setting of a zero-noise and in the absence of any confounding factors, such as patient's movements, breathing, perspiration, etc.

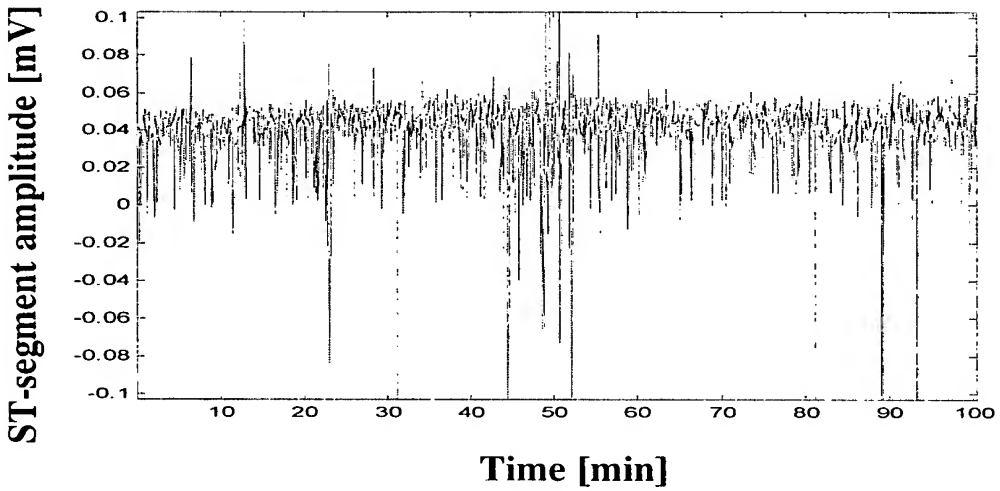


Figure 1. Time series of consecutive amplitudes of the ST-segment in a patient presented to the Emergency Department with Chest Pain

To further illustrate the differences between the method of Selker et al. and the Applicant's method, the following time series has been constructed using a computer random number generator, which produces a sequence of random numbers, with normal distribution, zero mean and unit variance. Assuming that each sample point represents one serial measurement of a primary element (for instance, ST-segment

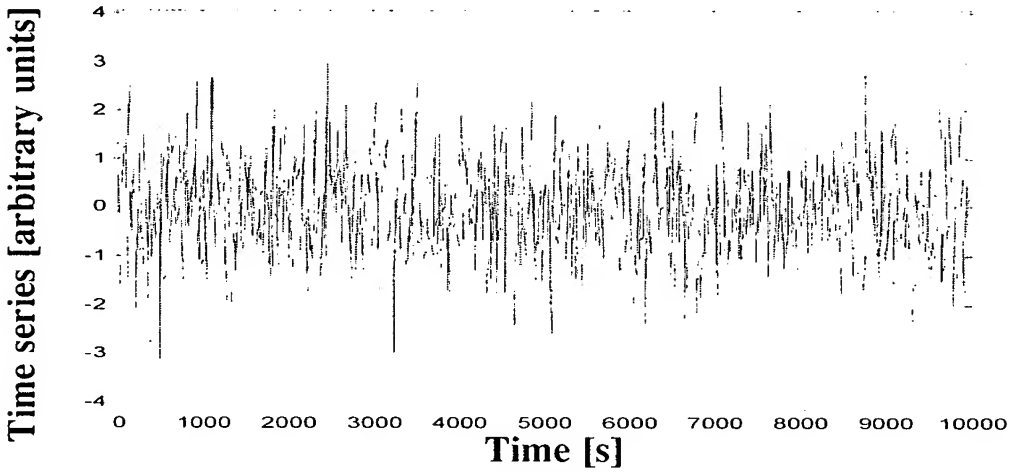


Figure 2. Time series of random numbers (Gaussian distribution, zero mean, and unit variance).

amplitude) and that the time interval between two consecutive time points is 1 second, the total length of the time series is 10000 seconds (Figure 2).

Since a real-life time series of primary ECG elements represents a combination of random noise and multiple periodic and non-periodic processes, the first 4000-sec segment has been modified by adding a periodic function, as follows: $y=0.7*x+0.6*\sin(1:4000)$, where x stands for the originally generated, random time series. Note that after this modification, the mean amplitude, variance, and the general structure of the first 4000-sec segment remain indistinguishable from the rest of the data by visual inspection (Figure 3).

However, spectral analysis of this segment using Fourier transform shows a clear spectral peak at 0.025 Hz (Figure 4), which is absent in the rest of the data (Figure 5). Thus, although the amplitude and the variance of the data seem visibly indistinguishable in the first 4000-sec segment and the rest of the data, the structure of this segment is clearly different. This structural difference between the first 4000-sec segment and the rest of the data would be missed by Selker's method (which only uses the amplitude of the data and a few other standard statistical estimates), but it would be identified by the Applicant's method, which analyzes the structure of the time series using a multitude of coefficients obtained from one of the mathematical methods described in the Applicant's disclosure.

Note that the mathematical methods described in the Applicant's disclosure have been previously used in time-series analysis of ECG signals (for example, in pattern recognition, feature extraction, and data compression). The novelty of the Applicant's invention is to adapt these methods, for the first time, for the **analysis of the time-series of the primary elements derived from the signal instead of the original ECG signal (which is equivalent to a higher-order time-series analysis).**

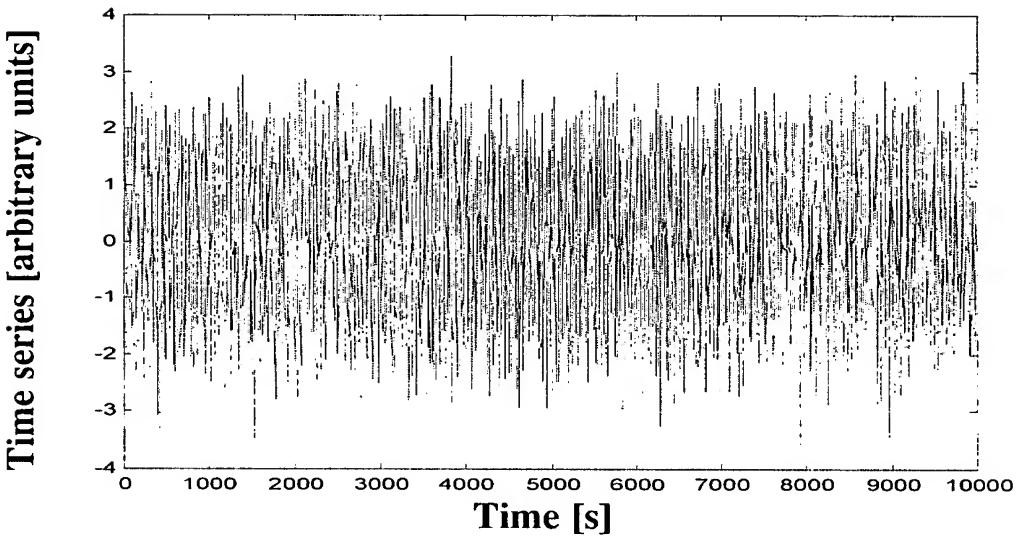


Figure 3. Time series shown in Figure 1 with the first 4000-sec segment modified. See text for details.

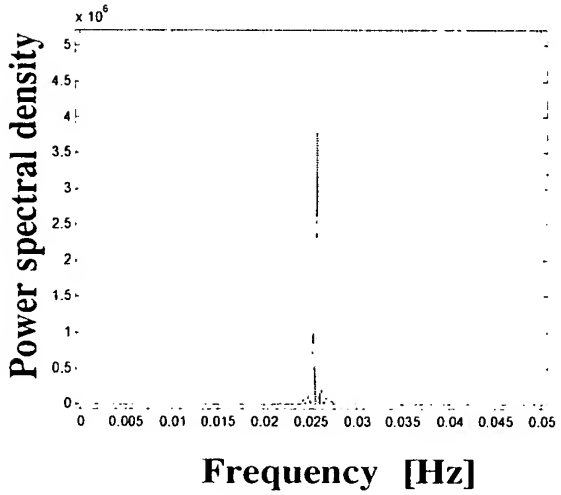


Figure 4. Power spectrum of the first 4000-sec segment of the time series shown in Figure 3.

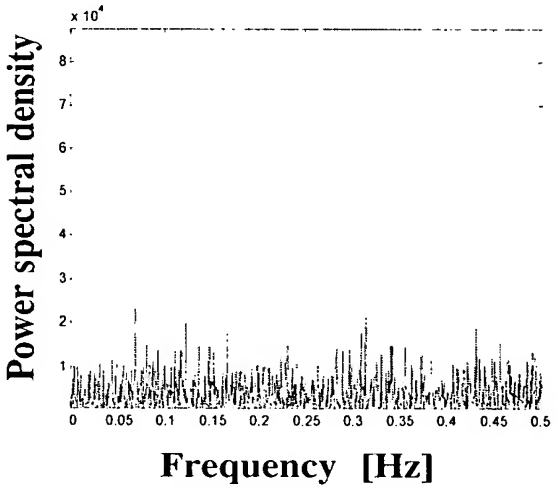


Figure 5. Power spectrum of the last 4000-sec segment of the time series shown in Figure 3.

Summarizing, the key differences between the Applicant's method and that of Selker et al. are:

1. The Applicant's method characterizes the structure of the time series by using a multitude of the coefficients derived with the use of one of the mathematical tools described in the Applicant's disclosure. In contrast, the method of Selker et al. does not analyze the structure of the time series. It only relies on the comparison between the current and one previous time point.

2. The Applicant's method analyzes the structure of the time series using a non-trivial adaptation of the mathematical tools (i.e. orthogonal and non-orthogonal decomposition) for time-series analysis. Selker et al. use a standard statistical analysis which can only detect a few, a-priori selected statistical estimators (such as changes in the amplitude above or below a certain threshold).

End of Examples

Paragraph 6 of the Official Action rejects Applicant's claims 1-6, 8, 12-19, 21, 25-31, 33, 35, 49, 53-56, and 59 under 35 U.S.C. 103(a) as unpatentable over Selker et al. (5,724,983). The Official Action states "The method steps of the above claims are considered to follow obviously from the normal workings of the Selker Device. Further, to use multiple computer systems would have been obvious since such would allow for analysis of more than one patient, such as in a hospital setting."

Applicant respectfully submits that the above-described differences between the Selker et al statistical analysis and Applicant's dynamic analysis are not trivial and were not obvious to those skilled in the medical arts at the time of Applicant's invention. Time series analysis is much more complex than the statistical analysis used by Selker et al. and was not understood or considered to be feasible by those skilled in the medical arts. Applicant's invention is widely recognized in the medical arts as being a departure from conventional wisdom and is a significant advance in the field. Confirmation of such advance in the art is provided by the Expert Opinions of five (5) highly respected experts in cardiac electrophysiology as set seen below under "**Expert Opinions**."

Expert Opinions

In 2002-2006, Applicant asked several experts to write what they think of "Pelex" (Applicant's acronym for his method and apparatus covered by this application) and gave each of them a list of questions. Later when Applicant created a web-site (www.pinmed.net), he asked each of the experts if they agree that he put their opinions on the web-site, and they responded in the affirmative. These experts were all well aware of the Selker et al. system since it had been marketed for some time prior by GE Medical Systems Technologies.

(1) "There is a need for such a system; I am not aware of any other system like this one. This system takes ECG analysis into another dimension. Instead of "linear" approaches, which use small lengths (3-10 sec) of ECG, this method allows serial comparisons of long segments of data, which provide robust characterization of data. This approach provides much more information than the traditional, short-term 12-lead ECG (which is 50-years old); it provides a tool to study dynamics of heart rate variability, restitution, etc. I would be very interested in using this system in my research. In particular, I would be very interested in analyzing dynamics of repolarization along with the cycle length. Some potential applications are:
ECG fingerprinting,
Normal patterns
Patterns altered by disease
Patterns altered by drugs
Monitoring changes in the course of the disease
Monitoring changes due to pharmacological agents
Autonomic nervous system effects."

Robert L. Lux, PhD, Professor of Medicine, Cardiovascular Research and Training Institute, University of Utah, Salt Lake City, Utah, NIH-sponsored Program Director, SCOR in Sudden Cardiac Death, Scientific Chairman and Board Member of the International Society for Computerized Electrocardiology, grant reviewer for the NIH, Member of the Editorial Boards of several Scientific Journals, Author of a number of scientific publications.
Phone: (801) 587-9529, Fax: (801) 581-3128, lux@cvrti.utah.edu.

(2) "Pelex is a great clinical tool for management of atrial fibrillation, palpitation syndrome, long QT-syndrome, QT-evaluation in patients with antiarrhythmic drugs. Pelex is also a great research tool. There is a need for such a system like Pelex, and I never saw a system like this one."

Raul Weiss, MD, FACC, Clinical Cardiac Electrophysiologist at Ohio State University, Partner and Clinical Cardiac Electrophysiologist at the MidOhio Cardiology and Vascular Consultants, Inc. (one of the leading and largest cardiology practices), Columbus, Ohio, Board-certified in internal medicine, cardiology, and electrophysiology, Member, North American Society of Pacing and Electrophysiology, American Heart Association, Fellow, American College of Cardiology, Principal Investigator for a number of clinical trials including NIH and industry-sponsored trials, author of over 80 scientific publications, Phone: 614/262-6772, FAX: 614/262-0435, rulyw007@aol.com.

(3) "Pelex saves a lot of emergency visits for cardiac and syncope patients. Pelex can replace Holter Monitoring, event monitoring, and loop recorders."

Samir Saba, MD, Director of the Cardiac Electrophysiology Program at the University of Pittsburgh Medical Center, Assistant Professor of Medicine, University of Pittsburgh Medical Center, Principal Investigator of several clinical trials, Recipient of research awards from the American College of Cardiology, Author of a number of scientific publications. Phone (412) 647-2762, sabas@msx.upmc.edu

(4) "I would be very interested in using this system in my practice, research, and clinical trials. There is a need for such system. I am not aware of any other system as this one."

David Schwartzman, MD, Director, Atrial Arrhythmia Center, Associate Professor of Medicine, Director, Cardiac Electrophysiology Laboratory, Presbyterian University Hospital, University of Pittsburgh Medical Center, Member, UPMC Technology Assessment Committee, Advisory Board Member, Biosense/Webster, Inc., Medtronic, Inc., Cardima, Inc., Zynergy Cardiovascular, Inc., Innercool Therapies, Inc., Principal Investigator of a number of Clinical Trials, Author and co-author of more than 200 scientific publications and 4 US Patents.
Phone: (412) 647-2762, Fax: (412) 647-7979, schwartzmand@msx.upmc.edu

(5) "Some ideas for uses of the Pelex system are:
Predictor of arrhythmia (VT/VF) onset using HRV, PVC's, changes in the sinus rate. Preventive responses are possible including an increase in atrial pacing, etc.
Follow-up for drug interaction, such as flecainide (QRS duration), sotalol/ dofetilide (QT duration), amiodarone (QT interval),
Telemetry for Implantable Loop Recorders to send data on arrhythmias via Internet,
High-tech event recorder and telemetry via Internet to notify MD office about bradycardia, etc., will eliminate the need for telephone transmissions,
Monitoring silent ischemia (silent ST-changes) in diabetic patients to change medications,
Changes in thoracic impedance (respirometer) to predict arrhythmic onset
Changes in autonomic tone (HRV),
CHF monitor to evaluate changes in dp/dt,

Changes in ECG from previous templates."

Stephen A. Fahrig, MD, FACC, Chief, Division of Cardiology, Associate Professor of Medicine, East Tennessee State University, Johnson City, TN, Author of a number of scientific publications, Principal Investigator of several clinical trials. Phone: (423) 232-4860, FAX: (423) 232-4881, fahrig@mail.etsu.edu

End of Expert Opinions

The innovative nature and significance of Applicant's invention, and the urgent need for the invention are also recognized by the Center for Scientific Review Special Emphasis Panel that reviews requests for grants by the National Institutes of Health (NIH). A copy of NIH's July 14-15 review of Applicant's grant proposal is attached to this Amendment. Applicant has underscored particularly relevant comments in the review.

The many patents on techniques for monitoring and analyzing cardiac conditions also evidence the existence of a long standing need in cardiology to be able to identify problems as soon as possible. However, the earlier in the process of analysis of a patient's condition, the smaller the changes, and the more difficult they are to detect and analyze. The probability of an error is also significantly higher when the attempt at detection and analysis is early in the progress of the disease (when the changes are very small). Medical researchers (including Selker et al.) have confined therefore themselves to the standard statistical analysis and not ventured into dynamic analysis of small serial changes. The small changes detected by Applicant's invention can be very gradual or irregular, masked by noise and variability of multiple physiological processes, responses to stimuli and environmental factors. Detection of such changes is not simple and requires a non-trivial modification of advanced mathematical methods described in the Applicant's disclosure. The prior art statistical analysis of snapshots of the primary elements would miss the subtle gradual or irregular changes that are detected by Applicant's invention.

The difficulties associated with the application of standard (static) statistical methods of artificial intelligence to the time-series analysis of large datasets over prolonged periods of time have been summarized in a seminal article by Bengio Y, Frasconi P (An input output HMM architecture. Adv Neural Inform Process 7: 427–434, 1995):

> "Learning problems involving sequentially structured data cannot be effectively dealt with static models such as feedforward networks... Up until

Applicant's disclosure. The prior art statistical analysis of snapshots of the primary elements would miss the subtle gradual or irregular changes that are detected by Applicant's invention.

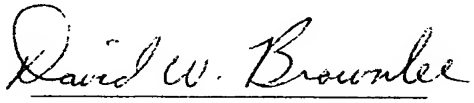
The difficulties associated with the application of standard (static) statistical methods of artificial intelligence to the time-series analysis of large datasets over prolonged periods of time have been summarized in a seminal article by Bengio Y, Frasconi P (An input output HMM architecture. Adv Neural Inform Process 7: 427–434, 1995):

> "Learning problems involving sequentially structured data cannot be effectively dealt with static models such as feedforward networks... Up until the present time, research efforts of supervised learning for recurrent networks have almost exclusively focused on error minimization by gradient descent methods. Although effective for learning short term memories, practical difficulties have been reported in training recurrent neural networks to perform tasks in which the temporal contingencies present in the input/output sequences span long intervals (Bengio et al., 1994; Mozer, 1992)." The authors conclude that "the effectiveness of the model on tasks involving large or very large state spaces needs to be carefully evaluated....learning long term dependencies in these models becomes more difficult as we increase the connectivity of the state transition graph."

It is therefore respectfully submitted that Applicant's invention is not only significantly different from the prior art like Selker et al, but also was not obvious to those skilled in the art.

In summary, Applicant respectfully submits that all the claims remaining in this application are allowable for the reasons given above. Accordingly, reconsideration and allowance are respectfully requested.

Respectfully Submitted,



David W. Brownlee
Registration No. 24,464
Attorney for Applicant

(412) 828-9397

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
ZRG1 CVS-K (10) B
July 14, 2005 - July 15, 2005

CHAIRPERSON

CHRONOS, NICOLAS A., MD
CHIEF MEDICAL AND SCIENTIFIC OFFICER
AMERICAN CARDIOVASCULAR RESEARCH INSTITUTE
ATLANTA, GA 30342

MEMBERS

BEISER, DAVID G., MD
ASSISTANT PROFESSOR
DEPT. OF EMERGENCY MEDICINE
UNIVERSITY OF CHICAGO
CHICAGO, IL 60637

BERRY, JOEL L, PHD
RESEARCH ASSISTANT PROFESSOR
DIVISION OF RADIOLGIC SCIENCES
DEPARTMENT OF BIOMEDICAL ENGINEERING
WAKE FOREST UNIVERSITY
WINSTON - SALEM, NC 27157

CHANDRA-STROBOS, NISHA , MD
PROFESSOR OF MEDICINE
CRITICAL CARE UNIT
JOHNS HOPKINS BAYVIEW MEDICAL CENTER
BALTIMORE, MD 21224

CHANDRASHEKHAR, YS , MD
ASSOCIATE PROFESSOR
DEPT. OF CARDIOLOGY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MN 55417

FAN, DALI , MD, PHD
STAFF CARDIOLOGIST
CARDIOLOGY
ST. FRANCIS HOSPITAL
ROSLYN, NY 11576

GILMAN, S. DOUGLAS, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF CHEMISTRY
LOUISIANA STATE UNIVERSITY
BATON ROUGE, LA 70803

GINTANT, GARY A., PHD
SENIOR GROUP LEADER
ABBOTT LABORATORIES
ABBOTT PARK, IL 600646119

GORMAN, JOSEPH H. III, MD
ASSISTANT PROFESSOR
DEPT. OF CARDIOTHORACIC SURGERY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104

GRAHAM, LINDA M., MD
PROFESSOR
DEPT. OF VASCULAR SURGERY
CLEVELAND CLINIC LERNER COLL. OF MED.
CLEVELAND, OH 44195

HOPKINS, RICHARD A., MD
KARLSON PROFESSOR AND CHIEF
CARDIOTHORACIC SURGERY
BROWN UNIVERSITY
PROVIDENCE, RI 02906

JAIN, DIWAKAR , MD
PROFESSOR
DEPT. OF CARDIOLOGY
DREXEL UNIVERSITY COLLEGE OF MEDICINE
PHILADELPHIA, PA 191921192

JEAN-CLAUDE, JESSIE , MD
ASSISTANT PROFESSOR
CASE WESTERN RESERVE UNIVERSITY
CHIEF OF VASCULAR SURGERY
VETERANS ADMIN. MEDICAL CENTER
CLEVELAND, OH 44106

JIANG, CANWEN , MD, PHD
SCIENTIFIC DIRECTOR
GENZYME CORPORATION
FRAMINGHAM, MA 01701

KARCHER, DONALD S., MD
PROFESSOR
DEPARTMENT OF PATHOLOGY
GEORGE WASHINGTON UNIV. MED. CENTER
WASHINGTON, DC 20037

KINSELLA, MICHAEL G., PHD
RESEARCH ASSOCIATE MEMBER
HOPE HEART PROGRAM
VIRGINIA MASON MEDICAL CENTER
SEATTLE, WA 98101

LAWSON, JEFFREY H., MD, PHD
ASSISTANT PROFESSOR
DEPT. OF VASCULAR SURGERY
DUKE UNIVERSITY MEDICAL CENTER
DURHAM, NC 27710

LEE, RANDALL J., MD, PHD
ASSOCIATE PROFESSOR
DEPT. OF CARDIOLOGY
CARDIOVASCULAR RESEARCH INSTITUTE
UNIV. OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA 941431354

LI, JOHN K-J, PHD
PROFESSOR
DEPT OF BIOMEDICAL ENGINEERING
SCHOOL OF ENGINEERING
RUTGERS UNIVERSITY
PISCATAWAY, NJ 08854

MANN, BRENDA K., PHD
DIRECTOR, PRECLINICAL R&D
PRECLINICAL RESEARCH AND DEVELOPMENT
SENTRX SURGICAL, INC
SALT LAKE CITY, UT 84108

MCFARLAND, RICHARD D., MD, PHD
MEDICAL OFFICER
CENTER FOR BIOLOGICS EVAL. & RESEARCH
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MD 20852

MCNULTY, PATRICK H., MD
ASSOCIATE PROFESSOR
DEPT. OF CARDIOLOGY
HERSHEY MEDICAL CENTER
HERSHEY, PA 17033

MCPHERSON, RICHARD A., MD
HARRY DALTON PROFESSOR & CHAIR CLINICAL PATHOLOGY
DIRECTOR, CLINICAL LABORATORY SERVICES
MEDICAL COLLEGE OF VIRGINIA
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23298

MOSESSO, VINCENT N. JR, MD
ASSOCIATE PROFESSOR
DEPT. OF EMERGENCY MEDICINE
UNIV. OF PITTSBURGH SCHOOL OF MEDICINE
PITTSBURGH, PA 15213

POLLARD, ANDREW E., PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
CARDIAC RHYTHM MANAGEMENT LABORATORY
UNIVERSITY OF ALABAMA, BIRMINGHAM
BIRMINGHAM, AL 35294

ROSENGART, TODD K., MD
PROFESSOR, HEAD OF CARDIOTHORACIC SURGERY
CARDIOTHORACIC SURGERY DEPT.
NORTHWESTERN UNIVERSITY
EVANSTON NORTHWESTERN HEALTHCARE
EVANSTON, IL 60201

ROSENSTRAUCH, DOREEN , MD, PHD
DEPT. OF CARDIOLOGY
UNIV. OF TEXAS HLTH SCI CNTR. & TX HEART INST.
HOUSTON, TX 77030

SAGAR, KIRAN B., MD
PROFESSOR OF MEDICINE
CARDIOLOGY
UNIV. OF WISCONSIN & HEART CARE ASSOCIATES
MILWAUKEE, WI 53215

SHUNG, K. KIRK, PHD
PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90089

SOROTA, STEVE C., PHD
SENIOR PRINCIPAL SCIENTIST
DEPT. OF NEUROBIOLOGY
SCHERING - PLOUGH RESEARCH INSTITUTE
KENILWORTH, NJ 07033

ST. GOAR, FREDERICK G., MD
DIRECTOR OF CLINICAL RESEARCH
CARDIOVASCULAR INSTITUTE
MOUNTAIN VIEW, CA 94040

TRACY, CYNTHIA M., MD
ASSOCIATE CHIEF
DIVISION OF CARDIOLOGY
DIRECTOR OF ELECTROPHYSIOLOGY
GEORGE WASHINGTON UNIVERSITY
MEDICAL FACULTY ASSOCIATES
WASHINGTON, DC 20037

VONDRISKA, THOMAS M., PHD
ASSISTANT PROFESSOR
DEPARTMENTS OF PHYSIOLOGY AND MEDICINE
UNIVERSITY OF CALIFORNIA, LOS ANGELES
LOS ANGELES, CA 90095

WILLIAMS, SHANNON P., PHD
VP, REGULATORY AFFAIRS & CLINICAL DEVELOPMENT
ADENOSINE THERAPEUTICS
CHARLOTTESVILLE, VA 22902

SCIENTIFIC REVIEW ADMINISTRATOR

BOERBOOM, LAWRENCE E., PHD
SCIENTIFIC REVIEW ADMINISTRATOR
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

GRANTS TECHNICAL ASSISTANT

PHILLIPS, ERIC G.
GRANTS TECHNICAL ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

2R44HL077116-02 SHUSTERMAN, VLADIMIR

RESUME AND SUMMARY OF DISCUSSION: ECG monitoring is a critical element in evaluation of patients with heart disease. The personal electrocardiographic system proposed in this application is aimed at wireless transmission of ECG data and automatic analysis using sophisticated computational pattern recognition strategies. The system has clear applicability in patients with arrhythmias or coronary disease. Excellent progress was made during Phase I, including successful development of a prototype and analysis of cardiac rhythm. In Phase II the investigators propose to develop a Beta prototype device and conduct a clinical trial. Well defined criteria for acceptance are described. The reviewers considered the device to be innovative and to have a high level of significance. A strong commercialization plan is presented. The reviewers did identify the apparent failure to blind the investigator responsible for comparing the tracings with respect to the technology being evaluated in Phase I as a weakness and strongly emphasized that this needs to be corrected in Phase II. Overall enthusiasm for the proposal was high.

DESCRIPTION (provided by applicant): The overall goal of the project is to design and develop an easy-to-use miniaturized Personal Electrocardiographic Expert (PELEX) system for real-time, on-site registration, analysis, and wireless transmission of electrocardiographic (EGG) data using structured pattern recognition approach for tracking changes in individual ECGs. The system will be designed both for clinical and non-clinical settings, including home-based monitoring, ambulatory follow-up, First Aid in emergency and mass casualty situations. For all these settings, a system that provides a real-time, on-the-scene ECG examination, analysis, and wireless transmission is urgently needed. Analysis of ECG changes in existing devices is limited, so that only a few parameters are compared to normal values or to the previous ECG recording. The completed system (Phase I and II) will include: 1) complete, in-depth analysis of ECG changes over time, 2) detection of subtle abnormalities that are hard to identify by visual inspection, 3) individually tailored analysis, 4) fast and efficient wireless communication between individual patient recorders, central computers, and health-care providers, 5) optimized collection, storage, and retrieval of serial data, and 6) comprehensive presentation of analyzed data to the health-care provider and appropriate feedback to the patient.

During Phase I, we have developed an Alpha prototype system and demonstrated its feasibility in the laboratory and clinical settings. The system has been enthusiastically received by cardiologists and spurred a strong interest from the device industry leaders. PELEX is the first all-in-one miniature (2x1x0.3 inch) wireless system that allows virtually any type of ECG testing, including gold-standard 12-lead ECG recording, stress-testing, 3/12 lead telemetry, ambulatory (Holter), event, and loop monitoring. PELEX has automatic bidirectional communication with central computer server, which performs complete analysis of ECG waveforms and an automatic, remote adjustment (individual tailoring) of monitored parameters.

In Phase II, we will refine and further improve the system to develop a Beta-prototype and conduct a larger-scale clinical trial both in a hospital and ambulatory setting to validate its performance against the best currently available systems and to receive feedback from medical professionals and patients. Safety and regulatory testing will be completed, and a 51O K application will be submitted to the FDA.

CRITIQUE 1:

Significance: Coronary Artery Disease remains the leading cause of mortality and morbidity in the U.S. in both men and women. It also accounts for more than 20% of all visits to Emergency Rooms. A cornerstone of evaluation in such patients is ECG monitoring, often in comparison to previous ECGs. This is not only time consuming but also delays therapies since many times comparison ECGs are not readily available. The Investigators propose the development of a compact, reliable, easy to use personal electrocardiographic system that provides for automatic analysis and wireless transmission of ECG data using structured pattern recognition, and individual ECG comparison. The potential clinical applications of this technology are considerable and are supported by the "testimonials" that are

attached to this proposal and are forthcoming from several thought leaders in the field of electrophysiology. It has obvious application for patients who are being monitored for arrhythmia detection. It can also be used for patients who are at high risk for arrhythmias to better predict those who are more likely to have ectopy based on T-wave alternans determination. It could also potentially be a much better tool for Holter monitoring since it would allow 12-lead analysis as compared to most Holter monitors that presently only record 2 or 3 ECG leads.

Finally, in a high-risk patient population, it is quite likely that it could minimize time-to-treatment for acute coronary syndromes.

Approach: The Investigators present the results of the Phase I proposal in which a prototype device was developed. They demonstrate that this device has an accuracy of QRS detection and a positive predictive accuracy of QRS detection of 99% and 97% as compared to existing MIT-100 and MIT-200 databases (resp.). This performance is comparable to that reported for several currently available systems. The positive predictive accuracy on noisy databases was expectedly lower at 92%.

The investigators also report preliminary data on wireless transmission and report successful and lossless and error-free transmission at <12/60 feet distance between the ECG recorder and the PDA/PC respectively. They were also able to demonstrate rapid and accurate ECG analysis and transmission within 20.3/20.01 seconds on a PD/PC, (respect). Transmission times required 5 seconds, establishing Internet connection via a dial-up modem took approximately 25 seconds, which yielded a total of 30 seconds for the Internet transmission and 50 seconds for the entire recording transmission analysis cycle. These results, listed above, fundamentally address specific AIM 1 & 2 of the Phase I proposal. The investigators also reported on preliminary clinical testing in 20 patients, in which results from the PELEX 04 system were compared to existing systems and to manual physician analyses. The criteria for acceptance were predefined as being an accuracy of QRS detection of >95%, error and ST amplitude measurement of <.02mv, an error in RT interval measurements of <10ms. The Investigators report on the results of 20 patients in whom Informed Consent was obtained. The results indicate that the accuracy of QRS detection was >95%. The error and RT interval measurement was 4ms. In summary, this study showed feasibility and accuracy of ECG recording and analyses using the PELEX-04 in a clinical setting. The Investigators, however, failed to describe how exactly the results were compared and whether the individual comparing the tracings was blinded to how the data were obtained.

Similarly, they report a study at Yale University where the PELEX system was used to evaluate the pro-arrhythmic effects of mental stress on cardiac repolarization. The patient population comprised of patients with ischemic or dilated cardiomyopathy and a history of spontaneous or induced ventricular arrhythmias: 33 patients were studied with Informed Consent. The investigators were able to demonstrate, as noted by other studies, T-Wave Alternans increased during mental stress. Also, peak amplitude of the T-Wave and the area under the T-Wave curve increased with mental stress indicating upsurge in proarrhythmic repolarization instability. Again, the Investigators failed to report how these data were analyzed or whether Investigators were blinded to the new technology being used.

The present proposal hopes to extend these preliminary observations and technology developments to better develop and construct a Beta prototype device consisting of a portable individual module providing complete onsite real-time analyses of the ECG waveform, a central server for analysis and storage of the serial data and a wireless bi-directional communication tool. The investigators define the criteria for acceptance of data similar to that previously noted, i.e. accuracy of QRS detection of >95% and lossless bi-directional wireless transmission of information. They describe in detail alternative hardware solutions and salient features regarding the specific components of the transmission systems being used. These features seem to be technologically and practically feasible though obviously warrant extensive evaluation and testing. The Investigators provide detailed data on algorithm analyses and data collection. These issues will be the primary goal of specific AIM 1.

Specific AIM 2 of this proposal will test the accuracy of the system for short-term (20 sec) one time ECG examination to demonstrate reliability and accuracy on 200 human subjects with cardiovascular disease and will be evaluated and the data from the PELEX compared to the existing system and by manual physician analysis. The investigators describe in detail how the protocol will be conducted. However, again they failed to describe the exact process by which the comparisons will be conducted and whether there will be any attempt made to blind the investigator reading the tracings to the technology that is being reported or compared. This remains an obvious limitation of the present protocol design and raises the obvious issues of conflict of interest. Insuring that data can be analyzed with the Investigator blinded to the technology used (to record the data) will enhance the reliability of the results.

In addition, this present study does not address the issue of differences in data recording in patients with varying chest physiognomy. For example, how reliable will this system be in obese patients with pendulous breasts? Although they clearly state that they will record patient age, sex, weight, height, symptoms and cardiac events, an obvious limitation of such a study will be if the data or the transmission quality is inaccurate in patients who have chronic obstructive lung disease, severe obesity, and other common conditions known to impair the EKG signal.

Also, since this will be based in homes, a comment on interference with or by cell phones/microwaves etc. would be useful. Comments on specifics of patient 'experience' would be useful, i.e. how many monitoring leads on the patient? How long are they worn?

Innovation: The study is creatively designed, with the technology being proposed being innovative and of considerable clinical significance.

Investigators: The Investigators are accomplished in the proposed field of investigation. They have previously received competitive funding and have been able to successfully complete the various grants for which they have applied.

Environment: The study will be conducted under the auspices of the University of Pittsburgh. The Investigators have adequate resources in terms of technology, financial, and clinical support to complete the proposed studies.

Milestones: The milestones suggested in this proposal are realistic and the progress in Phase I (as reported above) is commensurate with that originally proposed. A commercialization marketing strategy has been developed and appears to be clinically feasible.

Protection of Human Subjects from Research Risk: The Investigators present a comprehensive plan for protection of Human Subjects. They also provide a Table in which enrollment of women and minorities are well described. The reviewer notes that the clinical trial will be done primarily in Pittsburgh. The Investigators suggest that they will have a near 20% Hispanic population. This seems quite excessive for the geographical area in question and is not supported by data that is forthcoming from a quick review of the demographics of the Pittsburgh area. The Investigators need to better explain the basis on which they believe that 20% of the population will be Hispanic. G1A, M1A, C3A.

Data and Safety Monitoring Plan: The data and safety-monitoring plan presented is reasonable and provides for adequate patient safety and meets HIPPA guidelines.

Overall Evaluation: This comprehensive proposal strives to extend the results of the Phase I proposal in which a personal electrocardiographic expert system has been developed. The clinical potential for such technologies is considerable. The proposed investigation is flawed by the lack of blinding of clinical data that limits the rigor of the observations that have been forthcoming from prior studies. This is a limitation that can likely be overcome with not too much difficulty in the proposed clinical studies.

Budget: The proposed budget focuses primarily on salaries support for the PI an Engineer and a Scientist. A consultation cost request for an ergonomic design consultant seems somewhat excessive. Equipment costs are put forward and are well justified.

CRITIQUE 2:

Significance: On a clinical basis this product carries enormous potential significance allowing immediate and accurate assessment of subtle ECG changes in a wireless ambulatory setting. This can be applied to many cardiac conditions including arrhythmic and substrate abnormalities such as heart failure, etc... PinMed's technology has enormous market potential and has gathered corporate sponsors for marketing. This product could potentially address the major clinical need for real time recognition of patient clinical deterioration. This product would have major advantages over currently available products including wireless products that are now available which merely provide recordings without individualized analysis and rapid communication.

Approach: The overall goal of the project is to design a miniature Personal Electrocardiographic Expert (PELEX) system for real-time acquisition and processing of ECG's in a wireless, ambulatory setting. Work to date in Phase I, has lead to a prototype system that demonstrated feasibility in the laboratory and clinical settings. The PELEX is a miniature wireless system that allows ECG testing, (12-lead ECG, stress-testing, telemetry, ambulatory, event, and loop monitoring) with bidirectional communication with central computer server. The server provides analysis of ECG waveforms and remote adjustment of monitored parameters.

In Phase II, they plan to improve the system and develop a Beta-prototype to conduct a larger-scale clinical trial both in a hospital and ambulatory setting to validate its performance. Comparison will be against the currently available systems. They plan to complete safety and regulatory testing to submit a 51O K application to the FDA.

The approach is based on PinMed's patented algorithms which extract data from a series of ECG recordings to identify an individual baseline pattern and then track changes in this pattern using a mathematical approach. This approach has been validated mathematically and clinically. The investigators plan to initially produce 5 units for beta testing on which they will verify the hardware and firmware. They will then expand to 50 units for additional analysis. The companies involved in this phase (Niltronix and Zicon participated successfully in Phase I). The investigators will then test and debug the electrical schematics and mechanical components (lead attachment, charger connector, wireless communication) using Bluetooth technology. Performance of electrical, software and mechanical design will then be tested and regulatory requirements met. Finally, the hardware will be optimized and prepared for more broad production.

Innovation: This product is highly innovative and provides a significant advance over currently available ECG recognition and monitoring systems with huge potential in the wireless arena. The proposed system will provide: 1) analysis of serial ECG recordings using highly accurate pattern recognition algorithms for identifying individual patterns and tracking subtle changes not visible to the eye; 2) structured, multi-scale analysis, so that vital changes will be processed on-site in real time, with more subtle analysis in a central server; 3) individually tailored analysis, and 4) wireless communication between individual patient recorders, central computers, and health-care providers.

In Phase I, analysis of cardiac rhythm only has been achieved. In Phase II, the system will be improved to develop a Beta-prototype that will include 1) analysis of all vital ECG information on-site in a real-time and 2) comprehensive presentation of ECG changes for a medical professional and appropriate feedback to the patient.

Investigators: Dr Vladimir Shusterman is the President and CEO, of PinMed, Inc. He has received funding and patents in related technology. He has a team of experts available for product development.

Environment: Laboratory facilities required for the development and testing of software and hardware of the PELEX system are available at PinMed, Inc. This includes software and hardware development. Additional research partners provide expertise and space for product development.

Progress in Phase I: In Phase I, analysis of cardiac rhythm has been achieved

Commercialization Plan: Strong commercial interest exists and corporate partners have strongly expressed interest in product development.

Protection of Human Subjects from Research Risks: Adequate.

Inclusion of Women Plan: Adequate.

Inclusion of Minorities Plan: Adequate.

Overall Evaluation: This project has enormous potential and is highly innovative. The field of ambulatory monitoring has traditionally been restricted to arrhythmia management. More recent developments have suggested a role in heart failure management. This product does not require sophisticated implants and handles data in an ambulatory wireless setting. The patient populations listed in the application probably underestimate the true potential of this system. In summary, innovative, well thought out, highly applicable and doable.

Budget: No concerns

CRITIQUE 3:

Significance: The investigators propose continued development of a structure pattern recognition approach for ECG data recording, analysis and transmission (termed PELEX) that they have successfully built into an initial prototype during their Phase I funding period. The goal of this Phase II application, in addition to continued development, is to conduct a large-scale clinical trial that will allow performance comparisons against the best available systems. A significant strength of the overall proposal is that the analysis is considered in terms of parsed components whose implementation can be achieved locally, in real-time near the recording source, or can be achieved with distributed computing approaches via offsite computational approaches that will allow identification of parameters associated with serial dynamics. The proposal is well written. The need for alternatives to visual analysis that are sufficiently rigorous to control methodological errors in this research are important. To the extent that there is a weakness in the proposal related to its significance, background information associated with this highly developed research area is limited in the proposal.

Approach: The investigators propose aims to (1) develop and construct the beta prototype, (2) test the accuracy for short-term (20 sec) one time ECG examination in 20 subjects with cardiovascular disease (CVD) and (3) test accuracy on 50 subjects with coronary artery disease (CAD). An overall strength of the proposal is that specific criteria for acceptance in each of the implementation steps are included. The criteria are appropriate, and seem likely to confirm or negate the ability of the PELEX approach to compete with existing technologies. Another attractive aspect of the approach is that the investigators carefully consider alternative designs throughout the proposal. An example of this attention to research detail involves the dual-processor system used in Phase I development to control power consumption in the device via operation in a master-slave mode. Similarly, issues related to transmission rates are considered carefully, with emphasis on system construction that insures flexibility to accommodate a range of transmission strategies.

While care is take in the consideration of component design, the most significant strength of the overall approach involves the careful segmentation of parameters into groups that require more and less

rigorous computational strategies for determination. The investigators refer to Scale I parameters as those that can be obtained by straightforward and low-cost signal analyses. These are parameters such as RR or QT intervals that can be identified from the acquired records using techniques such as signal differentiation once noise issues are resolved. The Scale I parameters are then further analyzed using principal component analyses that involve mathematical decomposition into a series of orthogonal basis functions with coefficients for Scale II. Further decomposition of serial data using a similar approach will be performed for Scale III. Here, the transition from Scale I to Scale II and II induces computational overhead that will be managed by distributing tasks. The approach is elegant, specific and robust. Preliminary work in the analyses of responses to rapid pacing and isoproterenol-induced beta-adrenergic stimulation that established T-wave alternans supports the ability of the investigative team to complete the proposed studies. Furthermore, consideration of statistical issues and sample size calculations strongly support the overall approach.

Innovation: The main innovation of the proposal involves the mathematical decomposition strategy for the Scale I and Scale II analyses. Specific engineering steps for ECG recordings and archival for data transmission are not especially innovative as components, although their integration for this application is necessary and therefore innovative.

Investigators: The expertise of the investigative team supports their ability to complete the proposed studies. Shusterman from PinMed will supervise and coordinate all aspects of the project, which will be a strength given the commitment to the Phase I project that led to the successful design and implementation. Schwartzman and London at the University of Pittsburgh will participate in the clinical trials, which is also a strength. Partners for hardware development, software development, regulatory issues and commercial transition have been identified and their participation is also a strength.

Environment: No concerns.

Progress in Phase I: Phase I was highly successful. This proposal includes thorough description of revenue allocation in Phase I that support the proposed allocation for Phase II. The criteria for acceptance in Phase I were systematically considered in advance of moving to the Phase II proposal. Consistency in those criteria with those of the present application suggests a high likelihood for success. Productivity during Phase I is also evidenced by one publication and three patents (or applications) resulting from that support.

Commercialization Plan: The commercial plan is strong. Virtually all of the 5.8 million outpatient department visits with primary diagnosis of CVD in 1999 required dynamic ECG examination. The investigators clearly demonstrate a market that PELEX will serve. PELEX has been demonstrated to Medtronic, Medrad and GE HealthCare by PinMed. The PI has significant experience on consulting with companies in this device industry and the overall team has collaborative experience with company startup. Furthermore, the investigators carefully consider the technical advantages of PELEX to a wide range of available systems, indicating their awareness of barriers to market penetration that will have to be addressed for acceptance.

Overall Evaluation: This is a strong application in which the segmentation of analyses into parameters documenting the ECG dynamics at different scales suggests a high likelihood of success. The productivity of the research team and the commercialization plan are notable strengths.

Protection of Human Subjects from Research Risks: The risk to subjects is low.

Inclusion of Women Plan: Women will be included if the meet they inclusion criteria.

Inclusion of Minorities Plan: Minorities will be included if the meet they inclusion criteria.

Inclusion of Children Plan: Subjects who are less than 18 years of age will be excluded.

Budget: There are no budget concerns.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE. The risk to patients is low and is adequately addressed in the proposal.

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE. Women will be included.

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE. Minorities will be included.

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE. Children less than 18 years of age will be appropriately excluded, since the analysis and interpretation of ECGs in children is different from that in adults and the usefulness of the proposed system in children is uncertain.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.